REVIEW

MAYO CLINIC

Clinical Interpretation of Urine Drug Tests: What Clinicians Need to Know About Urine Drug Screens

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Abstract

Urine drug testing is frequently used in clinical, employment, educational, and legal settings and misinterpretation of test results can result in significant adverse consequences for the individual who is being tested. Advances in drug testing technology combined with a rise in the number of novel misused substances present challenges to clinicians to appropriately interpret urine drug test results. Authors searched PubMed and Google Scholar to identify published literature written in English between 1946 and 2016, using *urine drug test, screen, false-positive, false-negative, abuse,* and individual drugs of abuse as key words. Cited references were also used to identify the relevant literature. In this report, we review technical information related to detection methods of urine drug tests that are commonly used and provide an overview of false-positive/false-negative data for commonly misused substances in the following categories: cannabinoids, central nervous system (CNS) depressants, CNS stimulants, hallucinogens, designer drugs, and herbal drugs of abuse. We also present brief discussions of alcohol and tricyclic antidepressants as related to urine drug tests, for completeness. The goal of this review was to provide a useful tool for clinicians when interpreting urine drug test results and making appropriate clinical decisions on the basis of the information presented.

 ■ Mayo Clin Proc. 2017;92(5):774-796

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There have been increased concerns regarding the nonmedical use of prescribed drugs and rising trends in illicit drug use and dependence. In 2014, it was estimated that 27 million Americans aged 12 years and older (representing 10.2% of the population) have used illicit drugs in the past month; this is compared with 7.9% in 2004.[1] Urine drug testing is routinely used in clinical practice to rule out substance-induced disorders, confirm medication adherence, and identify substances in overdose situations. Employers and courts also perform drug tests to screen for illicit drug use. Despite the widespread use of urine drug tests (UDTs), there is little published information on how to correctly interpret the results of these tests. Incorrect interpretation of test results (false-positive or false-negative) can have significant consequences (eg, loss of job and incarceration). Unfortunately, there is evidence that there is a deficiency in clinician's knowledge about accurate UDT interpretation.[2,3] Regular use of UDT did not correlate with increased knowledge; therefore, the need for clinician education may be widespread.

The goal of this review was to provide an updated guide for clinicians that includes recent reports of agents that may cause false-positive results on common UDT immunoassays. We also expanded information on marijuana on the basis of recent legislative trends and included information on synthetic cathinones and cannabinoids. Our ultimate goal was to provide a concise reference that can be used in everyday practice by clinicians to accurately interpret UDT results that lead to appropriate therapeutic decisions.

LITERATURE SEARCH

Authors searched PubMed and Google Scholar to identify published literature between 1946 and 2016, using the following key words: *urine drug test, screen, false-positive, false-negative,* and *abuse*. In addition, individual drugs

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
www.mayoclinicproceedings.org ■ © 2016 Mayo Foundation for Medical Education and Research

of abuse discussed in the article were also used as key words. For completeness, we also identified relevant cited references in the initially identified publications. Publications that discussed urinary testing of substances in humans or human samples only were selected.

METHODS OF DRUG TESTING

Drug testing can be completed on various biological specimens including urine, blood, hair, saliva, sweat, nails (toe and finger), and meconium. Urine is the most commonly obtained specimen for drug testing due to its noninvasive route and ease of sample collection. Both parent drug and metabolites may be detected in urine specimens and are usually in higher concentrations than in blood or serum samples. Drug detection times are longer in urine (ie, 1 day up to several weeks) than in blood or serum samples.[4]

There are 2 main types of UDTs, screening and confirmatory tests. Initial drug tests or screens are performed using immunoassay technology and are conducted in the laboratory or onsite with point-of-care testing (POCT). Immunoassays allow for a large number of specimen screens to be completed and provide relatively rapid results.[5] Three main types of immunoassays are available: (1) enzyme-multiplied immunoassay technique, (2) enzyme-linked immunosorbent assay (ELISA), and (3) fluorescence polarization immunoassay. In general, immunoassays use antibodies to detect the presence of drug metabolites or classes of drug metabolites in the urine. Unfortunately, immunoassays will detect substances with similar characteristics, resulting in cross-reactivity leading to false-positive results.

An increasing trend, especially in pain management clinics and with clinicians treating patients with substance use disorders, is POCT in the office setting. It allows for immediate results onsite, allowing the clinician to discuss results with the patient in real time. These POCTs should be cleared by the Food and Drug Administration (FDA) and are usually waived by Clinical Laboratory Improvement Amendments. Visual analysis of the test result provides interpretation of the outcomes. At times, results may be difficult to read (eg, faint color and uncertain color), leading to subjective interpretation.[6] In addition, POCT has the same limitations as laboratory-based immunoassays and results should be used only to screen for a substance. Consumers who purchase POCT kits are cautioned against interpreting any positive preliminary results and confirmatory testing by a professional is recommended.

ARTICLE HIGHLIGHTS

- Immunoassays have many weaknesses that can result in false-positive and false-negative results. Understanding how to interpret urine immunoassays (eg, cutoff values, detection times, and false-positive results) is vital when ordering.
- All positive results on immunoassays need confirmatory testing (eg, gas chromatography/mass spectrometry).
- Testing for designer drugs (eg, synthetic cathinones and cannabinoids) is challenging secondary to continual changes in synthetic compounds and increasing number of novel substances.

All initial testing conducted with immunoassays need to be considered presumptive, and clinicians need to use clinical judgment, patient history, and collaborative information to decide whether confirmatory testing is necessary for optimal patient care. Gas chromatography/mass spectrometry (GC-MS) is considered the criterion standard in confirmatory testing and can identify specific molecular structures and quantifies the amount of a drug or substance present in the sample.[4] The GC-MS assessments must be conducted by highly trained personnel, are time-consuming and costly, and thus are reserved for confirming positive drug screens. Liquid chromatography/tandem mass spectrometry (LC-MS/MS) offers an alternative to GC-MS for confirmatory testing and may be more time-efficient. Confirmatory testing should always be conducted when making legal, forensic, academic, employment, or other decisions that have significant sequelae.

Cutoff Levels

Cutoff values for UDT define the concentrations needed to produce positive results for immunoassays and confirmation testing on GC-MS or LC-MS/MS. Cutoff levels were established to help minimize false-positive

results especially in workplace drug testing (eg, passive inhalation of marijuana causing positive results; poppy seeds ingestion causing positive opiate results). Results lower than the established cutoff values are reported as negative. Therefore, a negative result does not indicate that a substance is not present, but that the concentration was lower than the established cutoff concentration. Table 1 displays the federal mandated cutoff levels for the workplace developed by the Department of Health and Human Services.[7] Although clinicians should be aware of federal cutoff values for substances of abuse, they should recognize that the federal cutoff concentrations were established for use in the workplace in which higher cutoff concentrations may be necessary to avoid false-positive results.[4] However, in medical practice, lower cutoff values may be necessary particularly when testing for medication adherence. Clinical laboratories may use cutoff levels that are different from federal guidelines; thus, it is important that practitioners are aware of the values when interpreting results. In addition, clinicians may need to request a lower cutoff value to be used to minimize false-negative results; however, this may increase the rate of false-positive results. Furthermore, cutoff values were established for the adult population. Lower cutoff values may be necessary for infants due to a more dilute urine.[8] Urine osmolality tends to reach adult values after age 2 years.

Detection Times

Detection time or window is the amount of time a drug can be detected in the urine and still produce a positive result. To evaluate detection times of a drug or substance, both drug characteristics and patient factors need to be considered. Drug characteristics include half-life, drug metabolites, drug interactions, dosing intervals, low versus high dosage, chronic versus occasional use, and time of last ingestion. Patient factors that also can affect detection times include body mass, pH of the urine, urine concentration, and renal or liver impairment. Table 2 reports standard detection times for drugs routinely detected in the urine.[9-17]

EVALUATION OF A URINE SAMPLE

People misusing drugs commonly use various methods (eg, adulteration, urine substitution, diluting urine) to avoid detection. A basic understanding of urine specimen characteristics is helpful to the clinician when evaluating drug screen results.

Normal urine ranges from pale yellow to clear depending on its concentration. Specimens collected in the early morning have the highest concentration and therefore will

TABLE 1. Federal Workplace Cutoff Values[a,7]

Initial test analyte	Initial drug test level (immunoassay) (ng/mL)	Confirmatory test analyte	Confirmatory drug test level (GC-MS) (ng/mL)
Marijuana metabolites	50	Delta-9-tetrahydrocannabinol-9-carboxylic acid	15
Cocaine metabolites	150	Benzoylecgonine	100
Opiate metabolites			
Codeine/morphine[b]	2000	Codeine/morphine	2000
6-Acetylmorphine	10	6-Acetylmorphine	10
Phencyclidine	25	Phencyclidine	25
Amphetamine/methamphetamine[c]	500	Amphetamine	250
		Methamphetamine[d]	250
MDMA	500	MDMA	250
		MDA	250
		MDEA	250

[a]MDA = methylenedioxyamphetamine; MDMA = methylenedioxymethamphetamine; MDEA = methylenedioxyethylamphetamine.
[b]Morphine is the target analyte for codeine/morphine testing.
[c]Methamphetamine is the target analyte for amphetamine/methamphetamine testing.
[d]Specimen must also contain amphetamine at a concentration greater than or equal to 100 ng/mL.

TABLE 2. Approximate Drug Detection Time in the Urine[9-17]

Drug	Length of time detected in urine
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Chronic use (daily)	10-15 d
Chronic heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Phencyclidine	8 d
Synthetic cannabinoids	
Single use	72 h
Chronic use	>72 h
Synthetic cathinone	Variable

Adapted from *Mayo Clin Proc*, with permission.[12]

contain higher levels of the drug.[10] The temperature of the urine sample should be recorded within the first 4 minutes after collection and is usually between 90°F and 100°F.[18] Urine specimen temperature may stay at 90.5°F for up to 15 minutes. Although urine pH fluctuates throughout the day, it generally ranges between 4.5 and 8. Specific gravity normally ranges between 1.002 and 1.030. In normal human urine, creatinine concentrations should be greater than 20 mg/dL. Urine specimens that are of unusual color or that are outside the normal parameters for human urine may be due to medications, foods, or disease states (diuretics, strict vegetarian diet, high state of hydration).[19] It is imperative that documentation of these factors is included and be considered when the clinician is interpreting urine drug screen results.

Adulteration or dilution of the urine specimen should be suspected if the pH is less than 3 or greater than 11 or the specific gravity is less than 1.002 or greater than 1.030.[18] Urinary creatinine concentrations less than 20 mg/dL are indicative of dilute urine, whereas those less than 5 mg/dL combined with a specific gravity of less than 1.001 are not consistent with human urine.[10] Urine specimens outside of these ranges are due to adulterations or dilution attempts. Urine specimens adulterated with soap may also produce excessive bubble formation that is long lasting.[20] If the urine specimen appears to be adulterated or diluted, the second specimen for evaluation should be collected under observation.

Adulterants that have been used to mask a person's use of a substance include household items such as table salt, laundry bleach, toilet bowl cleaner, vinegar, lemon juice, ammonia, or eye drops. Several select commercial adulterants containing glutaraldehyde (Clean X), sodium or potassium nitrite (Klear, Whizzies), pyridinium chlorochromate (Urine Luck), and peroxide/peroxidase (Stealth) are used to mask drug use.[21] Most household adulterants, except for eyedrops, can be detected by routine integrity (ie, temperature, pH, specific gravity) measurements.[22] Commercial adulterants may mask the presence of drugs or their metabolites. Several dipstick tests (ie, AdultaCheck 4, AdultaCheck 6, Intect 7) are available for specimen integrity validation.[22]

SPECIFIC DRUGS TESTED IN THE URINE

Determining which drug to test for in a UDT panel depends on the clinical setting. Most panels include the 5 drugs required by federal workplace guidelines, which include amphetamines, cocaine, marijuana, opiates, and phencyclidine.[7] Benzodiazepines are commonly included in most UDTs. Clinicians working with patients with pain disorders should consider additional testing for semisynthetic (eg, oxycodone) and synthetic opioids (eg, fentanyl and methadone) (Table 3).[4] Mass-spectrometry–based definitive laboratory testing should be considered once to twice per year on the basis of the risk of assessment.[23] Below, we discuss common drugs of abuse encountered in the clinical setting and common false-positives and false-negatives with each

TABLE 3. Classification of Opioids[4]

Derivation	Opioid
From opium	Codeine, morphine, opium, thebaine
Semisynthetic	Buprenorphine, dihydrocodeine, heroin, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone
Synthetic	Fentanyl, meperidine, methadone, tramadol

screening test (Table 4).[12,17,18,24-112] The importance of confirmatory testing is emphasized to ensure an accurate and reliable UDT result.

Cannabinoids

Cannabis or marijuana generally refers to any part of the *Cannabis* plant and has been used throughout history for textiles, fuels, and medicines and for its euphoric effects.[11] The *Cannabis* plant contains approximately 460 active chemicals with more than 60 chemicals classified as cannabinoids. Delta-9-tetrahydrocannabinol (THC) is considered the primary active chemical responsible for marijuana's medicinal and psychoactive effects.

Currently, marijuana is the most widely used "illicit" substance in the United States, with almost 20 million Americans 12 years or older using marijuana in 2013.[113] Smoking or inhaling marijuana through cigarettes, cigars, water pipes, or vaporization is the most common route of administration primarily due to its rapid effects and ability to deliver high concentrations of the drug into the bloodstream.[114] Some users prefer the oral route of administration by mixing marijuana's oil base extract (hash oil) into common foods such as desserts, candies, or sodas.

Although illegal by the federal government, as of November 2016, 28 states plus the District of Columbia have approved marijuana use for medical purposes, and 8 states including the District of Columbia have approved marijuana for recreational use.[115,116] With state legalizations, it is important that clinicians inquire about medical and recreational marijuana use when ordering a drug screen to help with interpretation. It is important for users of medical or recreational marijuana to be aware that although approved by their state government, other entities (eg, federal systems, workplace, criminal justice systems, and schools) may still require a negative drug test result for marijuana. Furthermore, clinicians need to consider unintentional ingestion of marijuana especially in the presence of unexplainable neurologic conditions and food-borne illness. Both adults and children are susceptible to accidental ingestion of marijuana, especially through unlabeled food products.[117] Children may experience more profound effects due to the edibles containing unverified dosages, and adults who have never used illicit drugs may experience more adverse effects. Reports of accidental ingestions have increased markedly since the legalization of marijuana in various states, and clinicians need to consider ordering a UDT for THC when necessary.

Urine drug testing for marijuana is based on THC's main metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid.[7,118] Initial testing through immunoassay is sensitive to several THC metabolites and the federal cutoff level is 50 ng/mL although some laboratories may use a lower cutoff level of 20 ng/mL.[7] Confirmation testing via GC-MS or LC-MS/MS is specific for 9-tetrahydrocannabinol-9-carboxylic acid, allowing for a lower federal cutoff concentration of 15 ng/mL.[7,118]

Estimating the detection time for marijuana in the urine is multifaceted. Factors that influence detection of marijuana include route of administration, dosage and potency of marijuana, frequency of use, body mass, and one's metabolic rate. Cannabinoids are highly lipophilic and are extensively stored in lipid compartments throughout the body. Chronic use of marijuana will result in accumulation of THC in fatty tissues, resulting in slow elimination rates of marijuana metabolites.[118] Detection of marijuana can occur in the urine for greater than 30 days after cessation among chronic users,[118,119] whereas single exposure to marijuana in nonusers typically can be detected in the urine only up to 72 hours.[120]

A practical challenge with UDT for marijuana is determining acute versus chronic marijuana use. Researchers have looked at quantifying the glucuronide conjugates of THC and 11-OH-THC (using *Escherichia coli* β-glucosidase hydrolysis) as biomarkers for recent (<8 hours) marijuana consumption.[121,122]

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
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However, Lowe et al[121] found concentrations in the urine up to 24 days after cessation in a chronic heavy user, refuting the effectiveness of these biomarkers. With respect to driving under the influence, most states rely on blood levels to determine impairment.[123] However, blood concentrations can rapidly decline within the first hour because of rapid distribution into fat stores and first-pass hepatic metabolism.[124] In addition, Bergamaschi et al[125] found detectable THC concentrations in the blood after 30 days in 5 patients.

There are 2 FDA-approved prescription medication forms of THC. Dronabinol, a synthetic version of THC, and nabilone, a synthetic cannabinoid similar to THC, are indicated for chemotherapy-induced emesis and anorexia in patients with AIDS (dronabinol only).[60,61] Dronabinol will test positive for THC on UDTs, whereas nabilone tests negative for THC due to its distinct metabolites.[65] A challenge in patients receiving dronabinol is the inability to distinguish dronabinol from plant THC through confirmatory tests. Levin et al[126] conducted a study to determine whether testing for Δ^9-tetrahydroccanbivarin (THCV), a plant cannabinoid, in the urine would help distinguish the use of illicit plant marijuana use from oral dronabinol use. However, only 50% of participants who used cannabis heavily ($\geq$5 times per week) tested positive for THCV. The authors concluded that this test was not sensitive enough to test for either the presence or absence of THCV likely owing to variable strains of cannabis.

Medications reported to cross-react with cannabinoid immunoassays include proton pump inhibitors (PPIs),[64,127] nonsteroidal anti-inflammatory drugs (NSAIDs),[68] and efavirenz.[67,69] Literature describing the interference of PPIs with UDT is limited to 1 case report of pantoprazole and pantoprazole's package insert.[64,127] The mechanism for pantoprazole's interference with marijuana's UDT is unknown and it is unclear whether this is a class effect or limited only to pantoprazole. Prescribing information of other PPIs does not report this interference.

With respect to NSAIDs, Rollins et al[68] found that only 2 samples out of 510 samples produced false-positive results for cannabis on immunoassay, 1 in a patient who took a single daily dose of 1200 mg of ibuprofen and 1 in a chronic naproxen user. NSAID interference appears to be rare; however, secondary confirmation is warranted in patients using NSAIDs with unexplained THC results on immunoassay.

The cross-reactivity of efavirenz, a nonnucleoside reverse transcriptase inhibitor, on UDT for marijuana has been well documented.[67,69] The glucuronide metabolite (EFV-8-ether glucuronide) has been attributed to causing the false-positive result.

Surface contaminants with urine collections have also been shown to cause false-positive results in UDTs in newborns. Because of an increase in false-positive rates for THC UDTs in newborns, Cotten et al[63] investigated several commercial products and materials (eg, baby wash, wipes, diapers, and urine collection bags) to determine whether cross-reactivity was present. Several baby wash products produced a dose-dependent response on THC immunoassays, with many testing positive using a cutoff of 20 ng/mL but none reach the standard cutoff level of 50 ng/mL. It was discovered that nurses used different techniques to clean newborns before and during sample collection. This study highlights the importance of surface contaminants especially in the collection and analysis of urine in newborns.

A rising concern, especially with state approval of recreational marijuana use, is whether second-hand exposure to marijuana can result in positive drug screening. Several studies were conducted in the 1980s evaluating whether passive inhalation of marijuana would test positive on cannabis urine assays.[128-130] Most of these studies found detectable urine concentrations of THC's metabolites significantly below standard cutoff values. Since these studies were conducted, the potency of marijuana has significantly increased. In the 1980s, the potency of THC confiscated by law enforcement was around 3% whereas in 2014 the potency was approximately 12%.[131,132] With the rise in THC potency, Cone et al[133] evaluated the effects of passive inhalation with high-potency THC (up to 11.3%). The study placed 6 nonsmokers in a small room for 1 hour with smokers under the following conditions: (1) without air ventilation with participants

TABLE 4. Summary of Agents Contributing to Results by Immunoassay[a]

Substance	Potential positives (includes true- and false-positives)	Potential medications that may not be detected
Alcohol[24]	Short-chain alcohols (eg, isopropyl alcohol)	Not applicable
Amphetamines[25-50]	*l*-Methamphetamine (Vick's inhaler)[b]	Not applicable
	l-Deprenyl[c]	
	Amantadine	
	Aripiprazole	
	Atomoxetine	
	Benzphetamine	
	Bupropion	
	Clobenzorex[d]	
	Chlorpromazine	
	Desipramine	
	Dextroamphetamine	
	Dimethylamylamine	
	Ephedrine	
	Fenproporex[d]	
	Isometheptene	
	Isoxsuprine	
	Labetalol	
	Metformin	
	Methylphenidate	
	Methamphetamine	
	MDMA	
	Phentermine	
	Promethazine	
	Pseudoephedrine	
	Phenylephrine	
	Phenylpropanolamine	
	Ranitidine	
	Ritodrine	
	Selegiline	
	Thioridazine	
	Trazodone	
	Trimipramine	
	Trimethobenzamide	
Benzodiazepines[51-59]	Efavirenz	Alprazolam
	Oxaprozin	Clonazepam
	Sertraline	Lorazepam
Cannabinoids[17,60-70]	Baby wash products	Nabilone
	Dronabinol	Synthetic cannabinoids
	Efavirenz	
	NSAIDs	
	Proton pump inhibitors	
Cocaine[71-73]	Coca leaf tea	Not applicable
	Topical anesthetics containing cocaine	
Opioids/opiates/heroin[17,18,74-90]	Dextromethorphan	Buprenorphine
	Diphenhydramine[e]	Fentanyl
	Doxylamine[e]	Meperidine
	Heroin	Methadone
	Opiates (codeine, hydromorphone, hydrocodone, morphine)	Oxycodone
	Poppy seeds	Oxymorphone

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Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
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TABLE 4. Continued

Substance	Potential positives (includes true- and false-positives)	Potential medications that may not be detected
	Quinine	Tramadol
	Quinolones	
	Rifampin	
	Verapamil and metabolites[e]	
Phencyclidine[17,74,91-100]	Dextromethorphan	Not applicable
	Diphenhydramine	
	Doxylamine	
	Ibuprofen	
	Imipramine	
	Ketamine	
	Lamotrigine	
	MDPV	
	Meperidine	
	Mesoridazine	
	Thioridazine	
	Tramadol	
	Venlafaxine, *O*-desmethylvenlafaxine	
Tricyclic antidepressants[101-111]	Carbamazepine[f]	Not applicable
	Cyclobenzaprine	
	Cyproheptadine[f]	
	Diphenhydramine[f]	
	Hydroxyzine[f]	
	Quetiapine	
Synthetic cannabinoids[112]	Lamotrigine	Not applicable

[a]MDMA = methylenedioxymethylamphetamine; MDPV = methylendioxyprovalerone; NSAID = nonsteroidal anti-inflammatory drug.
[b]Newer immunoassays have corrected the false-positive result for Vick's inhaler.
[c]Converts to *l*-methamphetamine and *l*-amphetamine.
[d]Approved in Mexico. Not approved in the United States.
[e]Diphenhydramine, doxylamine, and verapamil (including metabolites) have been shown to cause positive results in methadone assays only.
[f]Reports of false-positive results occurred in serum only.
Adapted from *Mayo Clin Proc*, with permission.[12]

actively smoking marijuana cigarettes containing 5.3% THC, (2) without air ventilation with participants actively smoking marijuana cigarettes containing 11.3% THC, and (3) with active air ventilation with participants actively smoking marijuana cigarettes containing 11.3% THC.[133,134] None of the participants tested positive with an immunoassay (ELISA) cutoff level of more than 20 ng/mL in the room with ventilation. In rooms without ventilation, multiple immunoassays tested positive when using a 20 ng/mL cutoff value and 1 tested positive at the 50 ng/mL cutoff value (condition 2). Detection times to produce a positive screen (ELISA >20 ng/mL) ranged from 2 to 22 hours postexposure. Although 1 nonsmoker met the federal cutoff concentration and many with lower cutoff values, detection time was short and it was under harsh conditions (no ventilation) in which someone would be aware they were heavily exposed to second-hand smoke.

Central Nervous System Depressants

Opioids. "Opioid" is the term to describe all compounds that work at the opioid receptors in the central nervous system (CNS) and peripheral tissues. Opioids are primarily used for their analgesic properties, although they also have antitussive or antidiarrheal effects. Common prescription opioid medications include morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, methadone, and tramadol, while heroin is an illicit agent. The term "opiates" is used only to describe morphine and codeine, which are naturally

derived from the opium poppy seed.[135] Table 3 categorizes the opioid compounds according to sources of derivation.[4]

Opioid use has drastically increased in the past 10 to 15 years, and subsequently opioid misuse and abuse are also on the rise.[136] All prescription opioids have the potential for abuse and are Schedule II medications except tramadol, which recently went from unscheduled status to Schedule IV.[137] With the recent rescheduling of hydrocodone products from Schedule III to II, it is expected that there may be an increase in tramadol prescriptions due to ease of prescribing Schedule IV medications compared with Schedule II medications.[138]

Urine drug testing is one of many tools for safe prescribing of opioids with appropriate assessment and monitoring.[139,140] It is important for clinicians to be aware that UDTs may not detect all opioid drugs equally, and it is vital that clinicians ordering UDT for opioids know how to interpret results, are familiar with which agents their laboratory tests for, and understands opium metabolism (Figure 1).[136,141] Most conventional immunoassays use morphine as a single calibrator drug to set the threshold for distinguishing a "positive" or "negative" test result. Because cross-reactivity of antibodies between morphine and other opiates such as oxycodone, hydrocodone, hydromorphone, and oxymorphone is low, there may be a risk of false-negative results.[142] More advanced immunoassays or LC-MS/MS show higher specificity that can maximize detection for those agents.[142] Fentanyl, methadone, and buprenorphine have distinct differences in chemical structure compared with morphine; thus, there is no reactivity in commonly marketed morphine-specific immunoassays[89,143] and these require immunoassays that are specific for these compounds or LC-MS/MS.[76,80] In addition, some laboratories do not routinely test for semisynthetic or synthetic medication (see Table 3) in a standard opioid UDT unless specially requested. Clinicians must have an adequate understanding of their institution's laboratory immunoassay capabilities and/or the option for LC-MS/MS before using UDT.

Another clinical limitation with UDT for federal and Department of Transportation–regulated industry employees is the federal cutoff level of 2000 ng/mL with additional testing for heroin metabolite 6-monoacethylmorphine with a cutoff of 10 ng/mL use.[7] The cutoff level for opiate (eg, morphine and codeine) testing was raised from 300 ng/mL to 2000 ng/mL of morphine in 1998 in efforts to limit the large number of morphine and/or codeine positive results from poppy seed ingestion or routine prescription opiate use when screening for heroin abuse.[85,90] Unfortunately, using this high workplace drug testing cutoff level can result in negative test results, making it difficult for clinicians to interpret recent opioid use especially when testing for synthetic and semisynthetic opioids.[144] Clinicians who commonly prescribe opioid medications for chronic pain and use UDT for compliance monitoring and abuse detection may need to use the lower threshold

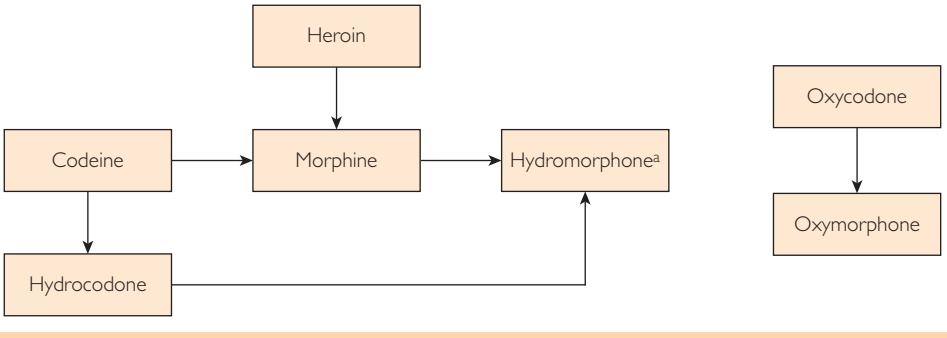

FIGURE 1. Metabolism of opioids.[136,141] [a]Morphine is metabolized to hydromorphone in very small amounts.

of 300 ng/mL. As clinicians, it is important that one is aware of their laboratory's cutoff value for opioids and when necessary may need to request additional testing at a lower cutoff. The most common reasons for opioid false-negative results are using incorrect testing for a specific opioid or there is insufficient concentration of opioid in the urine.[145]

A few nonopioid agents have been shown to cause false-positive results for opiates and are reported in Table 4. Quinolones, which are commonly prescribed antiinfectives, are widely reported to interfere with opiate immunoassays.[82,84] Meatherall and Dai[82] evaluated ofloxacin, norfloxacin, and ciprofloxacin for cross-reactivity on the enzyme-multiplied immunoassay technique II opiate immunoassay using a morphine threshold of 300 ng/mL. Ofloxacin was found to produce positive results, whereas norfloxacin and ciprofloxacin did not elicit positive results. Gatifloxacin also was found in a case report to provide a positive finding for opiates using the 2000 ng/mL cutoff level.[84] Rifampin or rifampicin also has caused false-positive results with opiate immunoassays.[77-79,87]

To understand opiate UDT, a proper understanding of specific opioid metabolism is essential. Studies have shown that clinicians struggle with interpreting opioid UDT results, which may be due to lack of understanding of opioid metabolism.[2,3] The following section reviews commonly prescribed opioids, their metabolic pathways (Figure 1), and their utility in UDT.

Morphine and codeine are both derived from opium. Codeine is metabolized to morphine and norcodeine. In the urine, all 3 compounds can be detected after codeine ingestion. Morphine is metabolized to 3-morphine-glucuronide and 6-morphine-glucuronide. Hydromorphone has been identified as a minor metabolite of morphine.[146] Codeine and hydrocodone metabolism can also produce small amounts of hydrocodone and hydromorphone, respectively, and should not be interpreted as indicators of hydrocodone or hydromorphone ingestion when high concentrations of codeine or hydromorphone are detected in the UDT.[147,148]

Heroin is rapidly metabolized to 6-monoacetylmorphine (6-MAM), which is further deacetylated to morphine. If heroin use is suspected, one can test for 6-MAM in the urine using a definitive method because the 6-MAM metabolite is specific only to heroin and not morphine or codeine. However, 6-MAM has an extremely short half-life of 36 minutes and is detected only up to 8 hours in the urine after heroin use.[149] In addition, street heroin may be adulterated with other opioids, such as acetylcodeine, making it difficult to differentiate between heroin, codeine, or morphine use.[24,150]

Oxycodone is frequently prescribed to treat pain and has been shown to have high abuse potential.[151] Oxycodone is metabolized into the active metabolite oxymorphone and moderately active metabolite noroxycodone.[152,153] About 13% to 19% of the dose is excreted as unchanged drug, 7% to 29% as oxycodone conjugates, 13% to 14% as oxymorphone metabolite, and an unknown amount to noroxycodone.[154] Large variability of metabolic ratio has been published in the literature identifying abnormal metabolite formation when considering ultra-rapid and poor metabolizers of oxycodone to oxymorphone.[153]

Methadone is a potent opioid with unique pharmacology; notably, it has a long elimination half-life, which makes it attractive for treatment of chronic pain and dependence on opioids and heroin.[135,155,156] About one-third of methadone is excreted unchanged in the urine and is metabolized to an inactive metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Although both methadone and EDDP are present in the urine, many methadone immunoassays detect only the parent compound, methadone. This can be problematic because patients occasionally spike their urine with their methadone prescription to generate a positive result on a UDT.[157] There are screening methods for methadone and EDDP and only 1 assay, Immunalysis's Homogeneous Enzyme Immunoassay (HEIA), tests for both with a cutoff of 300 ng for methadone and 500 ng for EDDP.[158] Moreover, testing for EDDP with GC-MS may be necessary with suspected adulteration and in patients who are rapid metabolizers of methadone. A few medications, including verapamil, diphenhydramine, and doxylamine, have been reported to cause false-positive screens for methadone and requiring secondary confirmation.[81,83,86]

Fentanyl transdermal patch is another widely used opioid mainly due to its convenient nonoral route, but it also poses a high risk of serious adverse effects including respiratory depression.[159,160] Fentanyl is extensively metabolized to its major inactive metabolite, norfentanyl.[135] Fentanyl has been shown to have high intrasubject variability over time and intersubject variability. In patients with pain disorders, the transdermal fentanyl excretion variability may be due to genetic polymorphism of the CYP3A4, skin absorption, and interactions with drugs used concomitantly that interfere with fentanyl metabolism.[161]

Tramadol is a weak opioid agonist that is commonly used for mild pain. It is a prodrug metabolized to an active metabolite *O*-desmethyltramadol and inactive metabolite nortramadol. Both these metabolites are further metabolized to inactive *O*-desmethylnortramadol.[162] GC-MS, LC-MS/MS, and other procedures to determine tramadol and its metabolites in the urine have been developed.[163] Clinical utility of tramadol drug screening may be important for clinicians to be familiar with as the use of tramadol increases.

Benzodiazepines. Benzodiazepines are widely prescribed for use as sedatives, hypnotics, anxiolytics, anticonvulsants, and muscle relaxants.[164] More than 15 benzodiazepines are commercially available for use in the United States; in addition, large numbers of other benzodiazepines are available in other countries including flunitrazepam, commonly referred to as the "date rape" drug. Because of their sedative properties, benzodiazepines are frequently misused and abused, and chronic use can lead to physiological dependence and addiction.

Urine drug testing for benzodiazepines is commonly used to check for medication adherence, evaluate abuse/misuse, or identify medications in overdose or emergency situations. Benzodiazepines are secondary to opiates in accidental or intentional overdose situations and are commonly prescribed with other sedating medications.[165] Because of the widespread use of benzodiazepines (eg, sedation in the emergency department setting), it is important that clinicians evaluate patient's medication regimen extensively when evaluating UDT results.

Interpretation of urine benzodiazepine immunoassays can be complex secondary to benzodiazepine's metabolic pathway (Figure 2), half-life, potencies, and the inability to differentiate between individual benzodiazepines.[166-168] Chronic use of diazepam, a long half-life agent, can be detected over 30 days in the urine, whereas triazolam, a short half-life drug, may be detected in the urine only for a day.[4] Benzodiazepines with short half-lives or those that are highly lipophilic (eg, alprazolam and diazepam) tend to have the most risk for abuse. Furthermore, there are 2 significant limitations of benzodiazepine immunoassays that may lead to false-negative results: (1) the immunoassay's inability to detect conjugated metabolites and (2) high cutoff values.

Most benzodiazepine immunoassays are designed to detect the free or nonconjugated forms of oxazepam or nordiazepam, which are common metabolites of several benzodiazepines (eg, diazepam, chlordiazepoxide, and temazepam).[167] However, many benzodiazepines are excreted as glucuronide conjugates (eg, lorazepam and alprazolam) and will not be detected by most immunoassays unless hydrolysis with beta-glucuronidase is performed on the urine before testing.[169-171] Most laboratories do not use this technique. Clonazepam is another benzodiazepine that may result in a false-negative result because it is primarily reduced to 7-aminoclonazepam and not converted to oxazepam or its conjugate nor does it cross-react well in the immunoassay screen.[172]

Cutoff concentrations of 200 or 300 ng/mL for benzodiazepines were initially established on the basis of standard dosages of older benzodiazepines such as diazepam, oxazepam, and flurazepam dosed between 5 and 20 mg/d.[57] Using a cutoff of 200 or 300 ng/mL often is too high for more potent benzodiazepines that are prescribed at lower doses such as lorazepam, alprazolam, and triazolam. Fraser and Meatherall[54,55] found that lowering the cutoff concentration of alprazolam and triazolam to 100 ng/mL along with enzyme hydrolysis increased positive results. In addition, West et al[172] recommended lowering the cutoff level to 40 ng/mL to detect clonazepam's main metabolite 7-aminoclonazepam.

Despite the high rate of false-negative results, medications that produce false-positive

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
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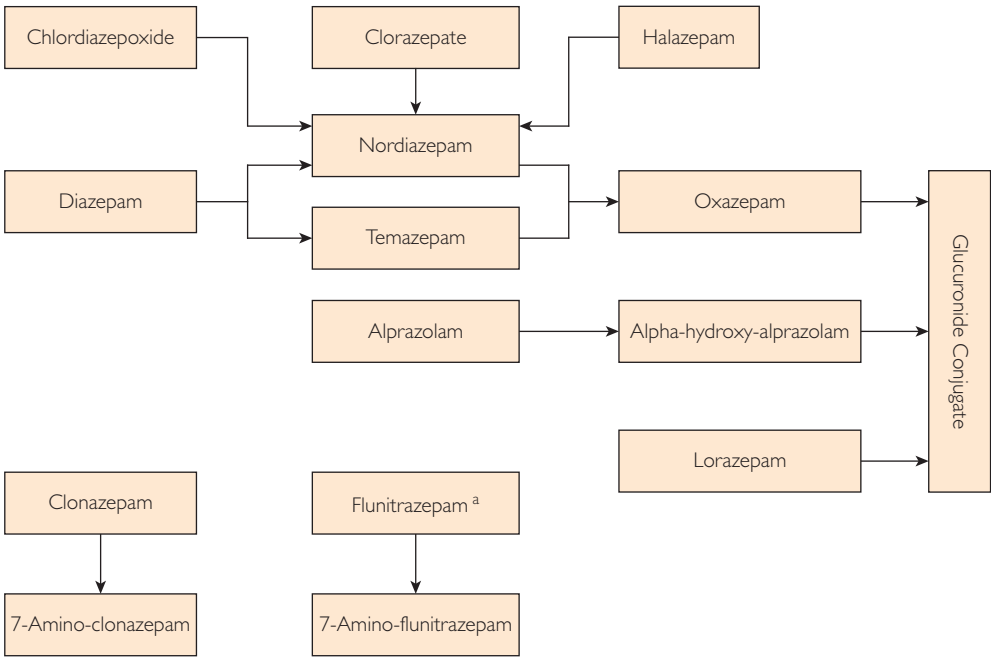

FIGURE 2. Basic metabolism of benzodiazepines.[166-168] [a]Flunitrazepam in not available in the United States.

results on the benzodiazepine immunoassays are minimal (Table 4). Sertraline, a commonly prescribed medication for treatment of depression, has widely been reported to cause false-positive results with benzodiazepine immunoassays with rates of 27% to 32% found in 2 retrospective studies.[52,56,58] Oxaprozin and efavirenz are additional agents that have also been found to interfere with the urine immunoassays.[51,53,59] However, efavirenz's interference has been found to occur only in the Triage 8 urine drug test and Drug Screen Multi 5 test.[53,59]

CNS Stimulants

Amphetamines. There are an estimated 1.6 million people aged 12 years and older (0.6% of the population ≥12 years) who reported using stimulants for nonmedical uses.[1] Among those who reported current use of stimulants, two-third reported abusing prescription stimulants but not methamphetamine. Amphetamines are commonly abused for their euphoric and stimulant effects, and prescription amphetamines have been favored by college students for their supposed "cognitive effects."

Amphetamine immunoassays are the screening tests most commonly associated with false-positive results due to the presence of other cross-reacting drugs and substances. It is difficult to develop antibodies that are specific to amphetamine and methamphetamines due to their structures. Methamphetamine also has 2 isomers (*d*-methamphetamine and *l*-methamphetamine) that contribute to issues with cross-reactivity and false-positive test results.[173] Amphetamine assays can detect amphetamines, its isomers (eg, dextroamphetamine), and other amphetamine-type compounds such as methamphetamine, methylenedioxyethylamphetamine, methylnenedioxyamphetamine, and methylenedioxymethylamphetamine as well as other metabolically produced amine-containing compounds.

Agents that have been commonly linked to false-positive amphetamine results include pseudoephedrine/ephedrine,[47] bupropion,[41] labetalol,[29,50] and ranitidine.[30,35,43] Bupropion's chemical structure is similar to those of amphetamines and contributes to the false-positive results.[41] Metformin has also been linked to false-positive results for amphetamines.[28] The mechanism is unknown

for metformin's interference, but the importance of confirmatory testing was stressed by one author to avoid negative consequences for patients. Additional medications and products that are not obvious culprits for causing positive results for amphetamines include selegiline and Vick's Vapor inhalers. Selegiline is metabolized into *l*-methamphetamine, *l*-desmethylselegiline, and *l*-amphetamine that contribute to its cross-interference with amphetamine assays. Selegiline's metabolites have also been detected in hair up to 4 weeks after a single oral dose.[174] Vick's Vapor Inhalers have been reported to contain 1% to 2.5% *d*-methamphetamine.[175] In Smith et al[175] report, *d*-methamphetamine and *l*-methamphetamine were not detected in urine at a lower level of quantification of 10 μg/L after 28 inhalations of Vick's Vapor inhalers. There were no positive test results for *d*-methamphetamine or *d*-amphetamine when GC-MS confirmatory testing was used. *l*-Methamphetamine was present in most urine specimens at 11 hours after the inhalation but at low concentrations (<250 μg/L). Lisdexamfetamine (Vyvanse) is a prodrug that is inactive before ingestion, which may lead to misconceptions that the drug will not be detected in UDT.[176] It should be noted that on activation in the gastrointestinal tract, lisdexamfetamine is converted to *l*-lysine and the active *d*-amphetamine and will be detected in the urine.

A popular dietary supplement containing dimethylamylamine (DMAA) also known as methylhexamine and geranium extract has been linked to a false-positive amphetamine screen.[48] DMAA has been marketed under the name OxyElite Pro (among others) for enhancing weight loss and athletic performance. It has been estimated that DMAA is present in more than 200 supplements despite reports of the agent's association with hemorrhagic strokes and death.[177-179] In an analysis by the Department of Defense, DMAA was found in 92.3% of the false-positive amphetamine samples that were then confirmed to be negative by GC-MS.[48]

Cocaine. Cocaine is a CNS stimulant extracted from coca leaves.[180] Similar to amphetamines, cocaine is often abused for its euphoric and stimulant effects. It can also produce anorexia, insomnia, and an increased attention span. Although illegal in the United States, some countries use coca leaves in teas, drinks, and other natural products. Ingestion of these products can cause positive results for cocaine UDT.

Urine testing for cocaine assesses the presence or absence of cocaine's primary metabolite, benzoylecgonine. Minimal cross-reactivity exists with drug screens for cocaine.[173] Although amoxicillin is reported from various Internet sources and review articles to produce false-positive results for cocaine, lack of evidence exists to support this finding.[181] Reisfield et al[182] tested amoxicillin's theoretical cross-reactivity for cocaine on 4 different immunoassays and found no false-positive results for cocaine metabolites. In clinical practice, cocaine is available for use as a topical anesthetic in otolaryngology and ophthalmic procedures. Topical and ophthalmic use of cocaine can produce true-positive results for cocaine in the urine.[183] However, other anesthetic agents such as benzocaine, lidocaine, procaine, and tetracaine are structurally distinct from cocaine and its metabolites and do not produce false-positive results on UDTs.[184]

Phencyclidine. Phencyclidine (PCP), a dissociative anesthetic, is 1 of the 5 mandated drugs of abuse in the Department of Health and Human Services guidelines for workplace UDT. Although PCP abuse declined in popularity in the 1980s and 1990s, there has been a revival of PCP use in the 2000s especially in combination with other illicit substances. In 2011, the Drug Abuse Warning Network found a 400% increase in emergency room visits for PCP from 2005 to 2011.[185] Frequently, abusers of PCP are dipping or spraying marijuana cigarettes with liquid PCP ("embalming fluid," "rocket fuel") often referred to as smoking "wet," "illy," or "fry."[186,187] Users of PCP-laced marijuana exhibit violent and aggressive behaviors, severe hallucinations, paranoia, and impaired motor skills.[188] In its pure form, PCP is a white crystalline power ("angel dust") and is commonly snorted, with effects seen in 2 to 5 minutes. Symptoms of intoxication usually last 4 to 6 hours; however, toxicity with large dosages can persist for 48 hours.[189] Detection

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
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time of PCP in the urine is approximately 8 days.

False-positive results for PCP on immunoassays have been reported to occur with agents that are structurally similar to PCP such as tramadol, dextromethorphan, diphenhydramine, and ketamine. Several case reports have shown tramadol's cross-reactivity to occur during tramadol toxicity, secondary to intentional overdose or misuse of the medication resulting in high tramadol concentrations in the urine.[94,96] Rengarajan and Mullins[98] reported that false-positive rates for PCP were 24% with dextromethorphan, 22% with tramadol, and 15% with diphenhydramine in urines that failed to be confirmed by GC-MS.[98]

Although a structural analog of PCP, there is a paucity of information on ketamine's cross-reactivity with PCP in the literature. Only 1 case report illustrates a false-positive PCP result after a 9-year-old boy received 400 mg of intramuscular ketamine for sedation before a magnetic resonance imaging scan.[100] Confirmatory test results were negative for PCP by GC-MS for this case. However, Weiner et al[190] reported negative PCP results on immunoassays in 3 patients with self-reported recent ketamine use. Further study is needed to assess ketamine's cross-reactivity with PCP due to increasing research and off-label use of ketamine to treat chronic pain and to rapidly reverse depression. Furthermore, new dosage formulations such as transmucosal, intranasal, and oral administrations of ketamine are currently in research and development and may result in increased use in the future.[191-193] Clinicians should inquire about ketamine usage in the presence of positive PCP results.

Medications that are not structurally similar to PCP that have been reported to cause false-positive PCP results on UDTs include venlafaxine and lamotrigine. Venlafaxine, a widely used antidepressant, has frequently produced false-positive results for PCP in urine assays both in standard and in overdose situations.[91,99] It is hypothesized that combined concentrations of venlafaxine and its metabolite, *O*-desmethylvenlafaxine, cause this cross-reactivity.

Lamotrigine, an anticonvulsant and mood stabilizer, is commonly listed as an agent to elicit a false-positive PCP result in UDT. However, only 1 case series correlates lamotrigine with false-positive results in 2 patients using Bio-Rad TOX/See Urine Toxicology screen.[92] In this case series, clinical history was used to rule out PCP use and no confirmatory testing was conducted. Further research is needed to clarify false-positive lamotrigine results on PCP rapid UDT.

A new drug of abuse, methylendioxyprovalerone (MDPV), a synthetic cathinone structurally similar to amphetamines and commonly referred to as "bath salts," has been found to cross-react with PCP on UDTs.[97] Several case reports noted an increased reactivity of PCP on urine immunoassays and negative confirmatory results in patients reporting recent bath salt ingestion. Macher and Penders[194] conducted a study in which MDPV was added to control urine and tested on the Synchron system. All urine samples tested positive for PCP with MDPV concentrations greater than 0.0031 mg/mL. Macher et al also examined mephedrone (4-methyl metcathinone) and no positive results for PCP were seen.[194]

Other medications reported to cause false-positive results for PCP are listed in Table 4.

Designer Drugs and Herbal Drugs of Abuse

Synthetic drugs, such as synthetic cathinones and synthetic cannabinoids, have become popular drugs of abuse especially among adolescents and young adults. In addition, herbal products, including *Salvia divinorum*, are popular. Once viewed as "legal highs," these drugs were readily available in head shops and gas stations and on the Internet. These agents became popular among people seeking a high due to their ability to avoid detection on UDT.

Drug testing for these agents can be challenging because of continual changes in synthetic compounds and an increasing number of newer substances. Testing for synthetic cathinones and cannabinoids is discussed in further detail. Salvia is briefly reviewed.

Synthetic Cathinones. Cathinones are naturally found in *Catha edulis* plant leaves, also known as khat. Khat is found in parts of Africa and has been known to have stimulant effects similar to those of cocaine, amphetamine, or 3,4-methylenedioxy-*N*-methylamphetamine

("ecstasy").[195] Cathinones have dopaminergic activities to increase dopamine levels beyond the effects produced by stimulant drugs.[196-198] Three of the most common compounds in bath salts are mephedrone, methylone, and MDPV (3,4-methylenedioxypyrovalerone). They either stimulate release of dopamine directly (mephedrone) or inhibit the reuptake of dopamine (methylone, MDPV).[199]

Bath salts, sometimes known as plant food, are synthetic cathinones that have gained popularity over the last 5 years. They are labeled "not for human consumption" to mask their intended purpose and avoid FDA regulatory oversight of the manufacturing process.[200] In 2011, the Drug Enforcement Administration added bath salts to its list of Schedule I substances in an attempt to curb manufacturing and distribution.[195] Unfortunately, new synthetic analogs used to manufacture bath salts are being constantly identified and make enforcement of laws difficult. Common product names that contain bath salts include Bliss, Cloud Nine, Vanilla Sky, and Zoom. Bath salts can be consumed by insufflation (snorting), ingestion, injection (intramuscular, intravenous), inhalation, or smoking, or taken sublingually or rectally.[201] Concentration of synthetic cathinones in the blood can vary depending on the method of administration.

An attractive marketing tool for these products is the claim that these products cannot be detected in routine drug screens. The fatal concentration of the drug in the blood has been reported to be approximately 400 ng/mL[199] based on postmortem data; however, the concentrations of the drug in the blood among fatal cases have varied for the 3 cathinone compounds ranging from 17 to 3300 ng/mL.[202,203] The parent cathinones are excreted rapidly in urine and are easily detected in biological materials. The elimination half-life in urine is approximately 12 hours and the excreted amount in urine can be influenced by urinary pH.[204]

There have been attempts at detecting synthetic cathinones in urine,[205,206] but the results have not been positive. Validation studies for the Randox Drugs of Abuse V biochip immunoassay, containing antibodies for mephedrone/methcathinone and 3'4'-methylenedioxypyrovalerone (MDPV)/3'4'-methylenedioxy-alpha-pyrrolidinobutiophenone, have been conducted.[205] The study showed that concentrations for mephedrone and MDPV were below acceptable criteria and had high negative percent bias. Of note, MDPV has been reported to cause false-positive results for PCP.[97] In the future, detection of specific cathinones will require higher specificity methods such as high-resolution, mass spectrometry.

Synthetic Cannabinoids. Synthetic cannabinoids are high potency, full cannabinoid receptor agonists at the CB_1 and CB_2 receptors compared with THC, which is a weak partial agonist at cannabinoid receptors.[207,208] JWH-018 is one of the most commonly abused synthetic cannabinoids found in products.[209] Other popular synthetic cannabinoid compounds include JWH-073, JWH-200, JWH-250, and CP-47,497 although hundreds of different synthetic cannabinoids exist.[210,211]

"Spice" or "K2" is a herbal blend of dried plant materials sprayed with synthetic cannabinoids. These products are typically sold as incense labeled "not for human consumption" to disguise their intended purpose and circumvent FDA oversight[200]; however, they are usually smoked by users to experience an extreme "high" believed to be more potent than marijuana.[212] Use of these products has grown in popularity since 2009 and is often perceived as safe and legal. In 2012, the Monitoring for the Future Study found that synthetic cannabinoids were the second most abused illegal substance behind marijuana among adolescents.[213] Synthetic cannabinoid use appeals to substance abusers for their inability to be detected for cannabis on UDTs.[214]

In July 2012, the Synthetic Drug Abuse Prevention Act was passed, making 5 structural classes of synthetic cannabinoid and their analogs a schedule 1 substance.[215] Additional synthetic cannabinoids were temporarily scheduled in 2013 and 2014.[216] Unfortunately, once a new synthetic cannabinoid becomes a controlled substance, illicit drug manufacturers promptly design new formulations in attempts to evade drug enforcement laws.

Several immunoassays and POCT have been developed to detect synthetic cannabinoids.

Mayo Clin Proc. ■ May 2017;92(5):774-796 ■ http://dx.doi.org/10.1016/j.mayocp.2016.12.007
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However, the continual development of new synthetic cannabinoids makes it difficult to keep up with current trends and test for specific synthetic cannabinoids in the urine. Synthetic cannabinoids are extensively metabolized and little to no parent drug is found in the urine.[209] Most assays are designed to detect JWH-018 and JWH-073 metabolites although many synthetic cannabinoids share the same structural pathway, allowing for broader detection on UDT. Because most synthetic cannabinoids have similar metabolic pathways, it is difficult to identify the parent compound ingested.

Another challenge with urine testing of synthetic cannabinoids is standardization of a cutoff value. Currently, there is no acceptable cutoff value, but assays may range between 5 ng/mL and 25 ng/mL. Barnes et al[217] studied cross-reactivity and sensitivity of the National Medical Service JWH-018 direct Elisa Kit designed to detect major metabolites of JWH-018. Seventy-three synthetic cannabinoids were analyzed for cross-reactivity. Their study found significant cross-reactivity of metabolites of other synthetic cannabinoids, most specifically JWH-200, JWH-073 N-(3-hydroxybutyl), JWH-073 N-(4-hydroxybutyl), JWH-019 N-(6-hydroxyhexyl), and AM-2201 N-(hydroxypentyl). Using the 5 μg/L cutoff provided the best sensitivity and increasing to 10 μg/L increased false-negative results by 12%. Their analysis also found limitations in the ability to detect newer synthetic cannabinoid compounds such as PB-22, RCS-4, RCS-8, XRL-11, and AKB48.

In addition, Barnes et al[217] evaluated 93 common medications and metabolites (eg, drugs of abuse, metabolites, prescription and over-the-counter medication, and chemicals with structural similarities) for cross-reactivity on the ELISA test. No samples, including marijuana, cross-reacted with the assay. However, the point-of-care test by Express Diagnostic lab, designed to detect JWH-018 and JWH-073 metabolites, reported that lamotrigine will cause a false-positive for their assay and will need confirmation.[112]

Because of limited studies, it is unclear the length of time the synthetic cannabinoids will be detected in the urine after using the products. Laboratories that offer synthetic cannabinoids testing estimate 48 to 72 after last use.[13,15]

Salvia. The Salvia plant is a member of the mint family with more than 900 species available.[218] Most species are commonly available in nurseries and used for decorative landscaping. However, the species *Salvia divinorum* is known to produce psychogenic effects when smoked or ingested and is listed as a controlled substance in approximately 20 states.[219] Salvinorin A is the main psychoactive component of Salvia that produces hallucinogenic effects. Testing for Salvia in the urine is limited to GC-MS or LC-MS/MS.[220] Because of expense and complexity, Salvia is not routinely tested.

OTHER AGENTS TESTED IN UDT

Alcohol

Ethyl alcohol is rapidly absorbed, metabolized, and eliminated after oral ingestion. Urine drug screening of alcohol intake is infrequently used in clinical practice. Blood tests or handheld breath devices are typically used in practice settings to assess alcohol intake. When testing for ethanol use is indicated, the alcohol metabolite ethyglucuronide (EtG) is preferred because it can be detected in urine for 2 to 5 days after alcohol intake.[221] Another metabolite ethyl sulfate may also be useful in detecting alcohol intake similarly to EtG although it is not used as frequently in POCTs. Incidental exposure to ethanol through hand sanitizers or mouthwash can produce positive UDT results. Using a ratio of EtG/ethyl sulfate may be useful in detecting alcohol intake versus incidental exposure.[222]

Tricyclic Antidepressants

Tricyclic antidepressants (TCA) can be used to treat depression, anxiety, neuropathic pain, and other related disorders. Despite their efficacy in treating multiple disorders, TCA are second-line treatments for most psychiatric disorders. They exhibit low tolerability (dry mouth, blurred vision, constipation, urinary retention) and have a high risk for toxicity in overdose ingestions. TCA toxicity mainly induces coma, cardiac conduction abnormalities, and seizures. High serum concentrations due to intentional or unintentional overdoses of TCA can be fatal. TCAs are considered to be toxic at more than 450 ng/mL[223] and at 1000 ng/mL plasma levels.[224] One advantage of using TCA is the

ability to monitor serum levels to assess medication adherence and detect presence during overdose/toxic situations.

Because of its 3-ring structure, other structures that contain similar ring structures frequently cause false-positive results on TCA urine or serum immunoassays. It is important to measure both parent and metabolite concentrations of tertiary TCA (eg, amitriptyline and imipramine) when interpreting therapeutic or toxic levels of these drugs. Metabolites such as nortriptyline and desipramine are themselves used for therapeutic purposes and may be detected separately. Common culprits include carbamazepine, cyclobenzaprine, and quetiapine (Table 4). In the emergency setting, rapid point-of-care urine immunoassays are preferable to quickly determine the cause and initiate treatment. In a study that compared the qualitative point-of-care urine immunoassays with quantitative serum chromatographic analysis, 7 out of 20 positive drug screen results corresponded to therapeutic serum concentration, 7 were subtherapeutic, and 6 were supratherapeutic or toxic.[225] This study showed the value of using quantitative serum chromatographic results versus qualitative point-of-care urine screens. It should be noted that clomipramine was positive in only 50% of patients using the Syva Rapid Test (Syva) and consistently negative using the Biosite Triage (Biosite) TOX urine assay. Most of the clomipramine dose in the urine is due to the 8-hydroxylated and glucuronidated metabolites and can trigger a positive immunoassay in the urine.[226] Clinicians should be aware that negative clomipramine results on a urine assay may fail to fully inform about clomipramine use.

CONCLUSION

Urine drug tests can be one of many valuable tools for clinicians in assessing unexplained toxic symptoms, monitoring adherence, treating patients with addiction, and prescribing controlled substances. However, it is important that clinicians have an appropriate understanding of UDT to minimize misinterpretation. Incorrect interpretation can result in legal consequences, unemployment, medications that are unwarranted, and possible dismissal from one's health care practice or school. Clinicians need to understand that initial testing from immunoassays offers presumptive results that can be confounded with potential false-positive and false-negative results. Moreover, providers need to be aware of cutoff limits used in UDT and decide whether lower cutoff levels are necessary. If necessary for clinical decision making, confirmatory testing with GC-MS and LC-MS/MS should be ordered to identify specific substances. Results of UDTs should be discussed with each patient and decision making surrounding UDT values should include a multidisciplinary team as well as the patient. Because of the complex nature of result interpretation and test ordering, it is critical that a close working relationship be established with the laboratory. Clinicians should be encouraged to discuss these issues with laboratory directors.

Abbreviations and Acronyms: **6-MAM** = 6-monoacetylmorphine; **CNS** = central nervous system; **DMAA** = dimethylamylamine; **EtG** = ethyglucuronide; **ELISA** = enzyme-linked immunosorbent assay; **FDA** = Food and Drug Administration; **GC-MS** = gas chromatography/mass spectrometry; **LC-MS/MS** = liquid chromatography/tandem mass spectrometry; **MDPV** = methylendioxyprovalerone; **NSAID** = nonsteroidal anti-inflammatory drug; **POCT** = point-of-care testing; **PCP** = phencyclidine; **PPI** = proton pump inhibitor; **TCA** = tricyclic antidepressant; **THC** = tetrahydrocannabinol; **THCV** = Δ^9-tetrahydroccanbivarin; **UDT** = urine drug test

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